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REVIEW OF ALL SUBMISSIONS ON THE HEALTH EFFECTS OF PCB'S IN CONNECTION WITH THE RULEMAKING TO ESTABLISH A TOLERANCE IN FISH AND SHELLFISH

BY

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INTRODUCTION

A rulemaking proceeding originating in Food and Drug Administratation's (FDA) Center for Food Safety and Applied Nutrition (formerly the Bureau of Foods) concluded that the tolerance for PCB's in fish and shellfish [21 C.F.R. §109.30(a)(7)] should be decreased from 5 ppm to 2 ppm. That conclusion was reached by use of a risk assessment which incorporated available rodent carcinogenesis bioassa data and human exposure data into a mathematical model to arrive at estimates of risk posed by exposure to PCB's. A linear extrapolation from high to low doses of the incidence of rat hepatocellular carcino and adenoma data, nodular hyperplasia data and hepatoma data assuming the imposition and enforcement of three tolerance levels - 5 ppm, 2 p and 1 ppm - was used to calculate that assessment. The conclusion wa that decreasing the tolerance from 5 ppm to 2 ppm would decrease the risk of cancer to the U.S. population. For example, using the total malignancy data from the National Cancer Institute (NCI) bioassay, th risk assessment estimated that the upper limit on the lifetime risk c cancer for heavy consumers of fish most affected by the tolerances would be reduced from 9.8 incidences of cancer per 100,000 of the population at a tolerance of 5 ppm, to 7.2 per 100,000 at 2 ppm. For average consumers of such fish the corresponding estimates were 3.7 a 2.7 incidences per 100,000 at 5 ppm and 2 ppm, respectively.

After a formal hearing on the economic impact of the rulemaking, the Agency requested that additional information on the health effect of PCB's be submitted for consideration by the Commissioner in reacht

the final Agency decision. This report describes the relevant data that were submitted and discusses the impact of those data on the risk assessment.

Over 100 scientific publications and reviews were submitted. A listing of those publications and reviews can be found in Appendix I. Only a portion of those 100 publications impact directly on the risk assessment. Those will be discussed below.

Generally, newly submitted data relating to the safety of PCB's to humans support the conclusion of the risk assessment. No data were submitted that significantly refute the findings of the risk assessment.

RESULTS AND DISCUSSION

Appendix II contains a listing of the twelve carcinogenesis studies submitted for consideration by the Commissioner. The listing divides those submissions into (a) studies cited in the risk assessment, (b) studies available but not cited in the risk assessment, and (c) studies not available at the time of the risk assessment (i.e., studies completed after the risk assessment). "Available" means that the study was in the scientific literature at the time that the risk assessment was written. Studies "not available" are those studies

which were not in the scientific literature until after the risk assessment had been completed.

Of the six studies cited in the risk assessment, only two had dat that were sufficient enough to be included in the actual extrapolatior of data [Kimbrough (1975) and NCI (1978)]. The data of a third study performed at Industrial Biotest Laboratories were considered supportiv of the results but were considered unreliable because of high mortality of the rats during the course of the study [Calandra (1975)] The remaining three studies cited in the risk assessment were deemed unreliable by the authors of the risk assessment because the studies were not of sufficient duration to adequately assess the risk of carcinogenesis.

There were four studies available but not cited in the risk assessment. Three of those studies were deemed by this reviewer to b of insufficient duration for an adequate assessment of carcinogenic risk [Nagasaki et al. (1972, 1974, 1975), Kimura and Baba (1973), and Ito et al. (1974)]. The remaining study by Wasserman et al. (1978) w of sufficient duration but contained only one dose group and one control group of six animals each. Nevertheless, this reviewer concluded that results of these studies support the results of the ri assessment because the effects observed were generally the same as those observed in the studies whose data were used in the risk assessment.

The third group of carcinogenesis studies consists of two studies which were published or completed after the date of the risk assessment. First, Weltman and Norbeck (1979) reported the presence of hepatic neoplastic nodules in rats that received 100 ppm 2',2',4,4',5,5' -Hexachlorobiphenyl in the diet for 24 months. Second, the Monsanto Company submitted results of a study in which rats were fed a diet containing 0,1,10 and 100 ppm Archlor 2254. Results showed an incidence of 3 of 26 animals and 14 of 26 animals with hepatic nodular hyperplasia in the 10 and 100 ppm groups respectively (observed 1 of 23 controls) and an incidence of 4 of 26 animals with hepatoma in the 100 ppm dose group [Levinakas (1981a)]. The results of the two studies are in agreement with the studies whose data were included in the extrapolation for the risk assessment.

Of the twelve studies listed in Attachment II, eleven had reported incidences of hepatoma, hepatocellular carcinoma or adenoma, or hepatic neoplastic nodules; endpoint histopathologies which were considered relevant by the authors of the risk assessment. These data support the conclusion that liver is a target organ for PCB's in the rodent and that hepatocellular carcinoma or adenoma can result from PCB ingestion - fundamental observations that influenced the assessment of risk. None of the data submitted refute those findings or the results of the risk assessment.

Appendix III contains a listing of the submitted data that suppor the notion that liver is a target organ in rodents, monkeys and human

beings. The listing is divided into those studies available and those studies not available at the time of the risk assessment. None of these studies were discussed in that risk assessment.

Of the studies listed in Appendix III and representative of disposition and metabolism data on PCB's in the rat, two which were available at the time of the risk assessment, reported increases in liver enzymatic activity and liver weight following a dosage of PCB's [see Ecobichon and Comeau (1975) and Bruckner et al. (1977)]. These two studies are among many reports reviewed by James et al. (1981) and submitted by the Chemical Manufacturers Association. This reviewer concludes that there is general consensus in the scientific community that PCB's induce rodent liver enzyme activity and cause significant increases in rodent liver weights.

Disposition and chemical analysis in the rat were studied in detail by Shimada and Sato (1980) who concluded that PCB-moieties are apparently covalently bound to hepatic macromolecules. This is particularly significant given the fact that PCB's have been shown to induce hepatocellular adenoma and carcinoma and underscores the importance of the liver in the disposition of PCB's in the rodent.

Induction of liver enzymes, enlarged liver, and liver pathologies were observed in non-human primates [Hori et al. (1980) and Yoshimura et al. (1981)] and indicate that the liver is also a target organ in those animals.

Human liver function as measured by the level of activity of certain enzymes generally associated with the liver and present in blood has been studied in workers exposed to PCB's. Seven of ten reports which were submitted reported abnormal liver function. Of the four available at the time of the risk assessment, three reported abnormal results. In addition, Wolff et al. (1981) postulated that PCB's induced the activity of cytochrome P-448 in livers of exposed electrical workers and Brown and Jones (1981) found abnormal incidence of liver cancer in another population of exposed workers. These data support the notion that the liver is a target organ for PCB's in humans.

The liver is a central issue regarding the toxicity of PCB's in rodent, non-human primate and man. There is strong evidence that PCB's produce heptocellular carcinoma and adenoma in the rat and evidence, albeit weak, that PCB's produced liver cancer in exposed workers. Therefore, the extrapolation of the rodent data and subsequent correlation of that data to man in the risk assessment is not refuted by any of the additional data.

Appendix IV is a listing of the relevant reproduction and teratology publications submitted. The data indicate that the rodent is more resistant to PCB-induced reproductive and teratogenic effects than the primate and mink. Indeed, a dose of 10 to 100 times that required in primates is required to induce observable reproductive or teratogenic effects in rodents.

The risk assessment discussed the report of Barsotti et al. (1976) which demonstrated that PCB's included in the diet of female Rhesus monkeys at 2.5 and 5.0 ppm (eight animals per dosage group) six months prior to mating, during gestation and four months after birth of offspring (while infants were nursing) produced significant toxic effects. All females conceived. Four of seven 5 ppm dosed females gave live births while seven of eight 2.5 ppm dosed females gave live births. During the four months of nursing, infants from both groups developed hyperpigmentation about the hairline. Analysis of the mothers' milk revealed concentrations of PCB's at 3.85 to 9.9 ppm (on a fat basis). Two infants from each group died following weaning. Prior to death, the infants developed all the signs of classical PCB poisioning (swollen eye lids, anorexia, scaley skin, acne, alopecia, loss of eyelashes, and loss of weight). It was concluded in the risk assessment that, ordinarily, adequate protection from such effects can be attained for children and adults if a level of toxicant producing no observable adverse effects is determined. Here the data do not permit establishment of such a "no-effect" level in monkeys. Also because the infant is undergoing tremendous growth and differentiation during this period it is possibly even more susceptible to PCB intoxication than is the adult. The assessment concluded, after review of data indicating the presence of significant levels of PCB's in human milk, "It is reasonable to predict that children exposed in such fashion may suffer an increased cancer burden from PCB's especially if dietary

contamination continues after childhood and throughout life; thus the risk estimates shown . . . [in this assessment] may underestimate ris in years to come."

The two studies in Rhesus monkeys completed after the completion of the risk assessment are a continuation of the study cited in the risk assessment [Allen et al. (1980) and Bowman et al. (1978)]. In t first, the mothers were fed a PCB-free, control diet for 1 year after the original study and then mated. Reproductive performance was normal. The second is a report of behavioral tests on the infants wh survived the initial study. Infants who had nursed on milk from mothers who had received 2.5 or 5.0 ppm PCB in their diets had increased errors in 5 of 9 learning tests conducted at ages 8 and 24 months even though they were no longer nursing. Tissue concentrations of PCB's decreased linearly in infants no longer nursing.

A third study was a reproductive study in mink [Bleavins et al. (1980)]. PCB's in the diets of mink for 2 years at 5.0 ppm and 2.0 pp produced complete reproductive failure.

The major concerns raised in the risk assessment, that the data Rhesus monkeys indicate that children may suffer an increased risk of cancer and potential risks other than cancer, still remain. A no observable effect dosage for the observed fetotoxic and reproductive effects still has not been established and the risk of cancer to infants who received significant concentrations of PCB's from their

mothers during gestation and after birth while nursing still may be underestimated. No submitted evidence allays those concerns.

Appendix V is a listing of relevant exposure data submitted. The report by Wickizer (1981) is a study done in Michigan of the PCB analysis of human milk from 1,057 women during 1977-1978. PCB contamination in milk was 1.496 ± 0.7986 ppm with a range from trace amounts to a maximum of 5.100 ppm. Examination of studies reporting analysis of human milk for PCB contamination reveals that in other areas where mothers are exposed to much lower environmental levels of PCB's the level of PCB's in milk is less. Dillon et al. (1981) reported PCB levels in 154 samples of milk collected in Quebec of 0.837 ± 0.529 ppm. Results of these studies support the uncertainty expressed in the risk assessment because they show that PCB's are present in human milk at nearly the same levels as those found in Rhesus mothers' that had received 2.5 or 5 ppm PCB in their diets. It is uncertain whether the in utero or postpartum (i.e., through nursing) exposure of the Rhesus offspring to PCBs was responsible for the toxic effects, mortality, and learning disabilities observed in the Rhesus infants.

A risk assessment prepared for the United States Congress, Office of Technology Assessment, [Crump and Masterman (1979)] was submitted for the Commissioner's consideration. That risk assessment leads to a tolerance level for PCB's in fish lower than the level calculated in the FDA risk assessment. This reviewer concludes that the Crump and Masterman risk assessment does not cast any doubt upon the validity of

the FDA risk assessment, because the two risk assessments are based c different assumptions. Moreover, Crump and Masterman based their ris extrapolation in part on the data from the lifetime feeding study by Calandra (1975). The authors of the FDA risk assessment deemed the Calandra study, which was performed at Industrial Biotest Laboratorie to be unreliable because of high mortality of the rats during the course of the study.

FINDINGS

1. No data were submitted that refute the conclusions of the assessmer of risk of carcinogenesis from PCB's.

2. Additional data were submitted that support the conclusions of the risk assessment. These include studies that show:

a. Liver is a target organ in rodents, non-human primates and humans.

b. Adverse liver function was observed in non-human primates and humans; increased liver weights were observed in rodents and primates.

c. Liver nodular hyperplasia, hepatoma and cholangichepatoma were observed in rats.

d. PCB-moieties were found apparently covalently bound to macromolecules in rat hepatocytes.

3. No data were submitted that refute or alter the conclusions and speculations of potential reproductive risks considered in the risk assessment.

4. A no adverse effect dosage level for the observed reproductive an toxic effects in Rhesus monkeys has not been determined. These effec raise concerns about PCB toxicity in addition to carcinogenesis.

5. In terms of reproductive effects, the subhuman primate appears to more sensitive than the rodent; more data are required to determine sensitivity of the primate to carcinogenic activity of PCB's.

6. The exposure to PCB's in fish and shellfish is in addition to the other human exposures already existing from milk, manufactured dair products, eggs, poultry and other sources.

CONCLUSION

The relevant data submitted in response to a request for additional data on health effects of PCB's support the findings and conclusion the risk assessment that a reduction of the tolerance for PCB's in and shellfish from 5 ppm to 2 ppm would reduce the risk of liver cancer.

APPENDIX I

Reference List of All Submissions Reviewed

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APPENDIX II

Carcinogenesis Data

a) Studies cited in the risk assessment

Species	Duration	# Dose Groups	Observations	Analysis*	Author
Mice	32 wks	3 plus controls	Nodular hyperplasia, hepatocellular carcinomas	Not of sufficient duration for carcinogenesis risk assessment	Ito et al.(1973)
Mice	11 mos	3 plus controls	Hepatoma	Not of sufficient duration for carcinogenesis risk assessment	Kimbrough and Linder(1974)
Rats	11 mos	3 plus controls	No observations reported in original risk assessment or other submitted materials	Not of sufficient duration for carcinogenesis risk assessment	Kimbrough et al. (1973)
Rats, Female (200 Sherman)	23 mos	1 plus controls (100 ppm) (diet)	Hepatocellular carcinomas (26 of 104 animals)	Used in original risk assessment	Kimbrough et al. (1975)
Rats 24/sex/ group(M & F) Fisher 344	105 wks	3 dose plus controls (25,50 & 100 ppm)	Hepatocellular carcinoma and adenoma	Used in original risk assessment	NCI(1978)
Rats 50/sex/ group(M & F) Charles River	24 mos	3 dose plus controls	Hepatoma, hepatic nodular hyperplasia	Considered unreliable because study of high mortality; but data was considered supportative of results	Calandra (1975)

APPENDIX II

b) Studies available but not cited in the risk assessment

Species	Duration	# Dose Groups	Observations	Analysis*	Author
Mice	32 wks	3 plus controls	Nodular hyplasia; carcinoma	Not of sufficient duration for carcinogenesis risk assessment	Nagasaki et al. (1972)
Rats, female	62 wks	4; no control	Hepatic adenomatous nodules	Not of sufficient duration for carcinogenesis risk assessment	Kimura and Baba(1973)
Rats, female (6 per dose)	28 mos	1 plus control	Hepatocellular adenoma (unclear significance)	6 animals in dose group; results inappropriate for adequate risk assessment	Wasserman et al. (1978)
Rats	52 wks	3 plus control	Nodular hyperplasia (all dose groups)	Not of sufficient duration for carcinogenesis risk assessment	Ito et al.(1974)

*Analysis by this reviewer based on the criteria used in the risk assessment.

APPENDIX II

c) Studies not available at the time of the risk assessment

Species	Duration	# Dose Groups	Observations	Author
Rats	24 mos	1 dose group(100 ppm diet)	Hepatic neoplastic nodules of questionable significance (details limited; published as an abstract)	Weltman and Norbeck(1979)
Rats	24 mos	3 dose groups; 1 control (1,10,100 ppm diet)	Hepatic nodular hyperplasia and Hepatoma; significant in high dose group only	Levinakas (1981a)

APPENDIX III

Evidence That Liver is a Target Organ for PCB

a) Studies available at the time of risk assessment

Type of Study	Species	Observations	Author
Epidemiology	Human Exposed to PCB's	Liver function; normal	Meigs *et al.* (1954)
	Human Exposed to PCB's	Liver function; abnormal	Hasegawa *et al.* (1972)
	Human Exposed to PCB's	Liver function; normal	Kitamura *et al.* (1973)
	Human Exposed to PCB's	Liver function; some abnormalities observed	Ouw *et al.* (1976)
Disposition	Rat	PCB's induce Hepatic enzymes	Ecobichon and Comeau(1975)
Disposition (diet)	Rat	Liver weight and enzymes activity; PCB's increased liver weights; hepatic microsomal enzyme activity	Bruckner *et al.* (1977)
Disposition (diet)	Rat and Primate	Rats eliminate 76% PCB's in 3 days days. Primates eliminate 2% in 3 days	VanHiller *et al.* (1975)

APPENDIX III

Evidence That Liver is a Target Organ for PCB

b) Studies not available at the time of the risk assessment

Type of Study	Species	Observations	Author
Epidemiology	Human Exposed to PCB's	Liver function; abnormal	Fischbein *et al.* (1979)
	Human Exposed to PCB's	Liver function; normal	Baker *et al.* (1980)
	Human Exposed to PCB's	Liver function; abnormal	Maroni *et al.* (1981 a,b)
	Human Exposed to PCB's	Liver function; abnormal	Kreiss *et al.* (1981)
	Human Exposed to PCB's	Liver function; abnormal	Smith *et al.* (1981)
	Human Exposed to PCB's	Liver function; abnormal	Chase *et al.* (1981)
	Human	Inducement of hepatic enzymes (cytochrome P-448)	Wolff *et al.* (1981)
	Human	Abnormal incidence of liver cancer	Brown & Jones (1981)
Disposition and chemical analysis	Rat	PCB metabolism; PCB-moieties found apparently covalently covalently bound to hepatic macromodecules	Shimada & Sato (1980)

APPENDIX III

Evidence That Liver is a Target Organ for PCB

b) Studies not available at the time of the risk assessment (continued)

Type of Study	Species	Variable Tested	Observations	Author
Subchronic	Rat	Liver pathology after 36 wks feeding 75 ppm PCB's	Liver necrosis	Johnson et al. (1981)
	Monkey	Liver pathology after feeding 40 ppm PCB's for 20 wks	Enlarged liver; unspecified liver pathology	Hori et al. (1980)
	Rhesus monkey	Liver enzyme activity after 7 mos of feeding 5 ppm PCB's	Increased activity of hepatic DT-diaphorase and benzo[a] pyrene-3-hydroxylase	Yoshimura et al. (1981)

APPENDIX IV

Reproduction and Teratology Experiments

Studies not available at the time of the risk assessment

Type of Study	Species	Variable Tested	Observations	Author
Teratology	Mice	Teratogenic effects; PCB's given by S.C. route	Cleft palates induced in dose-related manner; Fetal deaths and low conception at 5 mg/kg	Watanabe & Sugahara (1981)
	Mice	Hexachlorobiphenyl given by gavage; 2,4,8 & 16 mg/kg/day (14,28,56, & 112 ppm)	Increased incidence of cleft and hydronephrosis. A no effect level was not observed	Marks et al. (1981)
	Mice	Daily oral administration of 0.5 mg PCB's to pregnant dams on days 12-18 of pregnancy	Observed increases in fetal liver weights in treated groups	Mattsson et al. (1981)
Reproduction	Rat	Reproductive performance of dams fed 30 mg/kg of several commercial preparations of PCB's (equivalent to 600 ppm in diet)	No observed effects	Gellert and Wilson (1979)
	Rat	Fed 0,50,500 ppm PCB's to 3 groups of dams during pregnancy and until pups are weaned at	Litter size decreased in 500 ppm group; weights of pups from mothers	Collins & Capen (1980)

APPENDIX IV

Reproduction and Teratology Experiments

b) Studies not available at the time of the risk assessment (continued)

Type of Study	Species	Variable Tested	Observations	Author
Reproduction	Mink	PCB's in diets of mink for 2 years 2 groups; 5 ppm and 2 ppm	Complete reproductive failure	Bleavins et al. (1980)
	Rhesus monkey	Mothers fed PCB's at 2.5 and 5.0 ppm for 18 mos were fed control diets for 1 year	Adult monkeys had normal reproductive performance after 1 year	Allen et al. (1980)
Neurotoxicity	Rhesus monkey	Behavioral tests conducted on 3 surviving infants whose mothers had been fed 2.5 or 5.0 ppm PCB prior to, during and after gestation. Test conducted after infants had been weaned	PCB concentrations in infant tissues decreased linearly with time; increased errors in 5 of 9 learning tasks conducted between 8 and 24 mos in infants whose mothers had received PCB's	Bowman et al. (1978)

APPENDIX V

Exposure data

a) Studies available at the time of the risk assessment

Type of Study	Species	Observations	Author
Ecology Epidemiology	Human Fish	PCB contamination of rivers, ocean, soil and fish throughout Japan. Positive correlation of PCB's in regions and concentration of PCB's in human mink	Fujiwara, K. (1975)

b) Studies not available at the time of the risk assessment

Epidemiology	Human 1,057 women ages 17-44	PCB contamination of human milk: mean 1.5±0.8 ppm; PCB's present in milk presumed to be a result of environmental contamination. Concentration of PCB's at the same level that was fetotoxic in Rhesus monkeys	Wickizer T. (1981)
	Human Quebec 154 samples	PCB contamination of human milk: mean 0.837±0.529 ppm;	Dillon et al. (1981)

CERTIFICATE OF SERVICE

I hereby certify that a copy of the foregoing COMMISSIONER'S DECISIO in the Federal Register expected to be published May 22, 1984 and backgro thereto, re: Docket Number 77N-0080; PCBs in Fish and Shellfish, was mail this day, registered mail, postage prepaid to:

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